Cherubism: Case Report and Review of the Literature

Cherubism: Olgu Sunumu ve Literatür Derlemesi

Elif TARIM ERTAŞ,[a]
Fahrettin KALABALIK,[a]
Meral YIRCALI ATICI,[a]
Ömer DEMİRTAŞ[a]

[a]Department of Oral and Diagnosis Radiology, İzmir Kâtip Çelebi University Faculty of Dentistry, İzmir

Geliş Tarihi/*Received:* 26.04.2015
Kabul Tarihi/*Accepted:* 01.12.2015

Yazışma Adresi/*Correspondence:*
Fahrettin KALABALIK
İzmir Kâtip Çelebi University Faculty of Dentistry, Department of Oral and Diagnosis Radiology, İzmir
TÜRKİYE/TURKEY
kalabalikfahrettin@hotmail.com

ABSTRACT Cherubism is a rare autosomal-dominant disease characterized by bilateral painless enlargement of the jaws giving a cherubic appearance to the patient. The disease also affects tooth eruption, occlusion and mastication. Radiographically, the lesions are seen as bilateral, well-defined, multilocular, radiolucent osteolytic areas. Differential diagnosis includes fibrous dysplasia, central giant cell granuloma, keratocystic odontogenic tumor (including Gorlin-Goltz syndrome), brown tumor of hyperparathyroidism, ameloblastoma, odontogenic myxoma and aneurismal bone cysts. As the cherubism is a self-limiting disease and the lesions show spontaneous involution related to age, surgery for cosmetic reasons is preferred after puberty. In this report, we present a case of cherubism with a dental malocclusion that included the ectopic eruption and displacement of teeth caused by the lesions in a 15-year-old boy with the available literature.

Key Words: Cherubism; malocclusion; cone-beam computed tomography

ÖZET Cherubism çenelerin bilateral ve ağrısız genişlemesi ile karakterize, hastaya melek yüz görünümü veren, nadir görülen otozomal geçişli dominant bir hastalıktır. Hastalık aynı zamanda diş sürmesini, oklüzyonu ve çiğneme fonksiyonunu etkiler. Lezyonlar radyografik olarak bilateral, sınırları belirgin, multiloküler, radyolüsent osteolitik alanlar olarak izlenir. Ayırıcı tanısı fibröz displazi, santral dev hücreli granüloma, Gorlin-Goltz Sendromu'nda görülen keratokist odontojenik tümör, hiperparatiroidizmde görülen brown tümörü, ameloblastoma, odontojenik mikzoma ve anevrizmal kemik kistini içerir. Eğer cerrahi tedavi gerekli görülürse, kendi kendini sınırlayan bir hastalık olduğu için ve lezyonlar yaşla birlikte gerilediği için cerrahi işlem puberte sonrasına ertelenebilir. Bu çalışmada 15 yaşında erkek hastaya ait, ektopik erüpsiyonlar ve diş deplasmanlarına neden olan cherubizm olgusu, literatür bilgileri eşliğinde sunulmuştur.

Anahtar Kelimeler: Çerubizm; maloklüzyon; konik ışınlı bilgisayarlı tomografi

Turkiye Klinikleri J Dental Sci Cases 2015;1(4):223-8

Cherubism is a non-neoplastic, hereditary bone disease characterized by bilateral, relatively symmetric painless expansion, involving only the mandible or both mandible and maxilla.[1,2] The lesions result in the characteristic "cherubic" appearance with swelling of the cheeks and upward tilting of the eyes.[2] Its prevalence is 1 or less in 10,000 with a 2:1 female-to-male predilection.[3] Many cases of cherubism have been reported.[2] Patients are normal at birth; the expanding jaw becomes noticeable within the first few years of life, becoming increasingly larger until the beginning of adolescence.[4,5] The initial clinical signs of this disease commonly begin at

doi: 10.5336/dentalcase.2015-45883

about 2 years of age, but since children's faces are quite chubby, cases with only slight deformity may go undetected until the second decade.[1,6] Radiographically, the lesions appear as multiple, well-defined, multilocular, radiolucent areas with a soap bubble appearance, which often dramatically alter the shape and size of the jaw structures. The most common physical manifestations of cherubism are bilateral, painless enlargement of cheeks and the jaws.[1,7] Although, surgical management may be indicated in patients with serious cosmetic problems, most clinicians avoid any treatment until puberty because the disease is self-limiting and the lesions tend to stabilize or regress in puberty.[6,7]

The aim of this report is to present a case of cherubism with a dental malocclusion that included the ectopic eruption and displacement of teeth caused by the lesions in a 15-year-old Turkish boy.

CASE REPORT

A 15-year-old boy was referred to our clinic with a complaint of mastication disturbance and painless bilateral facial swelling. There was no history of cherubism in the other members of the family. Clinical examination showed a well-developed, cooperative healthy boy with bilateral symmetrical enlargement of the lower jaw and cheeks (Figure 1). There was no local tenderness and lymphadenopathy on palpation. Intraorally, anterior displacement of mandibular second molars was seen (Figure 2). He had no specific dental, medical or family history.

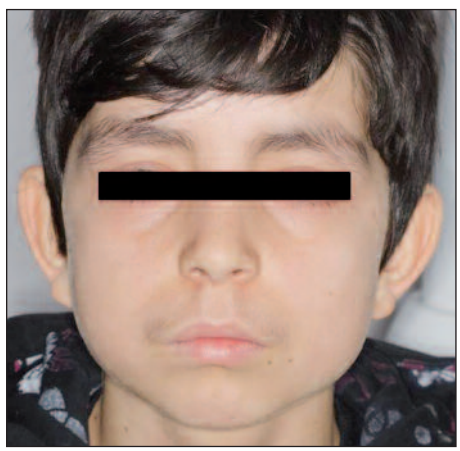

FIGURE 1: Photograph of patient showing frontal view of face with symmetrical bilateral mandibular swelling.

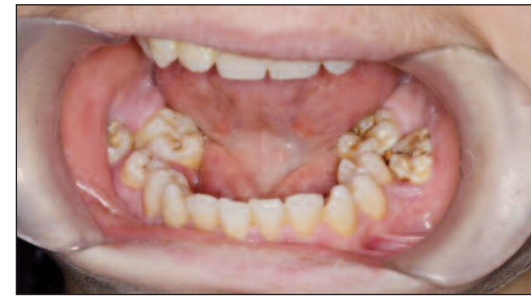

FIGURE 2: Intraoral view shows bilateral displacement of mandibular second molars to an anterior direction.

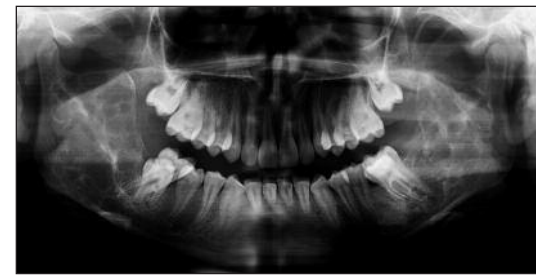

FIGURE 3: Panoramic radiograph with multilocular irregular radiolucency in the rami sparing the condyle and coronoid process.

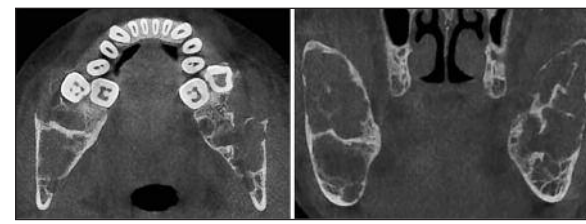

FIGURE 4: Axial and coronal slice sections depicting the extent of the lesion.

A panoramic radiograph showed bilateral, multilocular, radiolucent osteolytic areas, similar to soap bubbles in appearance. Lesions were extended from the ascending ramus to the body of the mandible, but the mandibular condyles were unaffected (Figure 3). After his parents signed an informed consent form recording their agreement, cone beam computed tomography (CBCT) determined the precise extent of the lesion and the involved anatomic structures along with the degree of destruction. CBCT scan showed bilateral, large,

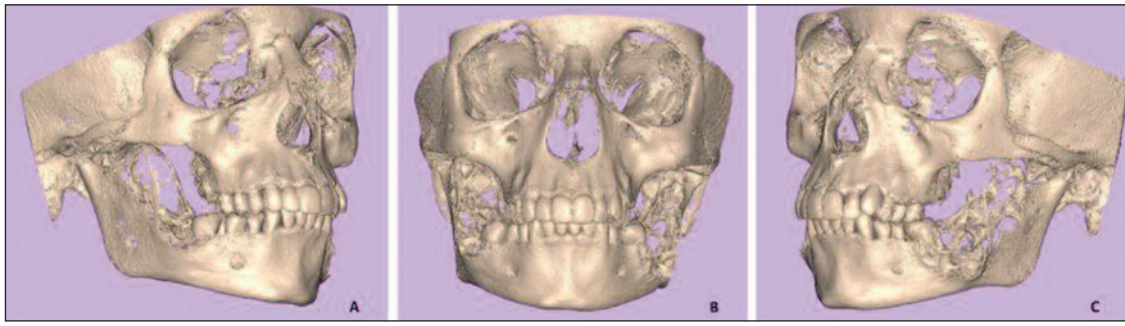

FIGURE 5: (A) Right profile, **(B)** frontal and **(C)** left profile three-dimensional Cone Beam Computed tomography (CBCT) scan of the mandible showing bicortical expansion of the lesions with perforation of the buccal cortex.

expansile, multilocular osteolytic lesions with perforation of the cortical bone at the angle and ramus of the mandible and displacement of the mandibular second molar teeth in an anterior direction (Figures 4 and 5). The mandibular canal was displaced inferiorly. Examination of the hand-wrist radiograph indicated that the patient was in the pre-peak pubertal period of growth. Parents of the patient were told that the disease might progress until puberty and then regress at the end of skeletal growth.

Based on clinical and radiographic features, the diagnosis of cherubism was established. The patient was referred to the orthodontic department for the complaint of mastication disturbance caused by displacement of the mandibular second molars. The patient was also referred to the endocrine clinic for calcitonin treatment.

DISCUSSION

Jones first described cherubism in 1933 as a familial multilocular cystic disease of the jaws. [8] It is a rare inherited benign bone disease that is transmitted as an autosomal dominant trait with 100% penetration in males and 50-70% in females. However, several sporadic cases have also been reported.[9,10] The normal bone is replaced by cellular fibrous tissue and immature bone in cherubism. The mandible is the most severely affected bone among the craniofacial component and deterioration affects the aesthetic balance of the face.[11] Mandibular involvement is commonly bilateral, but unilateral involvement has also been also described.[12,13] The maxilla is less commonly involved and the lesions are usually less extensive. It is always accompanied by mandibular lesions.[14] Bilateral swelling of the cheeks as a result of mandibular and maxillary expansion causes orbital manifestation and a tendency of the eyes to look upward.[15]

The etiology of cherubism is not known exactly.[16] Recent studies have identified mutations in the SH3-binding protein 2 (SH3BP2) gene on chromosome 4p16.3; these mutations are thought to be responsible for cherubism.[17] Genetic mutations may not be detected in 20% of affected individuals and this suggests possible genetic heterogeneity.[2,18] Cases of cherubism associated with other disorders such as Ramon's syndrome, Noonan's syndrome, Jaffe-Campanacci syndrome, fragile X syndrome and neurofibromatosis type 1 have been published.[2] A perivascular fibrosis leading to mesenchymal disorder and decreased oxygenation occurring during the development of the bone is the widely accepted theory for its pathogenesis.[19]

Classification of cherubism based on location and severity of lesions has been proposed by many authors. The latest grading system, proposed by Misra et al, is as follows:[16]

- Grade I: Bilateral involvement of the mandibular rami without signs of root resorption.
- Grade II: Involvement of both mandibular rami and maxillary tuberosities without signs of root resorption.
- Grade III: Aggressive lesions of the mandible with root resorption.

- Grade IV: Lesions involving both the mandible and maxilla with signs of root resorption.
- Grade V: Rare, massively growing, aggressive and extensively deforming juvenile lesions involving the maxilla and mandible.
- Grade VI: Rare, massively growing, aggressive and extensively deforming juvenile lesions involving the maxilla, mandible and orbits.
- Grade VII: Bilateral involvement of the mandible and/or maxilla associated with other abnormalities/syndromes.

The present case might be categorized as a grade 1 case of cherubism due to the fact that bilateral lesions occurred only in the posterior mandible without signs of root resorption.

Cherubism commonly affects children before the age of 6 years.[20] The clinical signs and symptoms are variable, and depend on the severity of the disease. Typical features of cherubism are bilateral, painless enlargement of the cheeks and jaws. Enlargement of the submandibular and, more rarely, the upper cervical lymph nodes have also been reported, but this usually occurs in patients less than 5 years of age.[8,21] In our case, we found no lymphadenopathy probably because the patient was older than 5 years of age. Not only massive deformity of the jaws, but also respiratory difficulty with maxillary involvement may be encountered in the severe forms of the disease.[22] Silva et al. reported a case of an 8-year-old boy who presented with severe cherubism in which the lesions progressed rapidly;[23] 17 months later he died due to pulmonary and gastrointestinal infections.

Dental problems such as anterior tooth displacement, root resorption, impacted or unerupted teeth and malocclusion have been frequently reported.[22,24] CBCT images showed intensive displacement of bilateral mandibular second molars and mild displacement of bilateral mandibular first molars and second premolars in our patient.

Radiographically, the disease appears as a well-defined multilocular, radiolucent osteolytic lesion of the jaws. The usual involvement of the disease begins at the angle of the mandible and extends into the ramus and body. In rare cases, condylar involvement may be seen. In most of the cases it causes thinning and expansion of the cortical plates. In severe cases displacement of the inferior mandibular canal and cortical perforation may be noted. Bilateral cyst-like lesions are usually limited to the mandible and maxilla, but rare cases of involvement of the zygomatic arches, temporal bone, orbit and condyles have been reported.[25,26] CBCT is very useful tool for the assessment of lesion dimensions, precisely the limits of the lesions, their components, behavior and the exact relation with surrounding structures in cherubism.[27] In our case, CBCT images showed bilateral, large, expansile, multilocular osteolytic lesions with expansion and perforation of the cortical bone at the angle and ramus of the mandible.

Differential diagnosis includes fibrous dysplasia, central giant cell granuloma, keratocystic odontogenic tumor (including Gorlin-Goltz syndrome), brown tumor of hyperparathyroidism, ameloblastoma, odontogenic myxoma and aneurismal bone cysts. Fibrous dysplasia more commonly occurs unilaterally and is not seen as multilocular radiolucency. Ameloblastoma, odontogenic myxoma, and aneurysmal bone cysts manifest as multilocular lesions in the mandibular ramus region and the lesions are definitely unilateral.[6,16] However the bilateral symmetric lesions, multilocular appearance, the anterior displacement of teeth and typical facial appearance are characteristics in cherubism that help with the differential diagnosis.[6] Multiple odontogenic keratocysts in Gorlin-Goltz syndrome may bear some radiographic similarity to cherubism, but this syndrome usually also causes skin lesions or rib abnormalities without the characteristic facial swelling.[28] The characteristic radiographic features of this disease may be more diagnostic than the histopathologic outcomes because central giant cell granuloma and brown tumor of hyperparathyroidism present a similar histological appearance with giant cells.[6,22] Bilateral cyst-like lesions are multilocular, well-defined radiolucent areas showing a soap bubble appearance

with an increase in bone septa characteristic of the irregular structure in cherubism.[1,29] Clinical features and radiographic findings are the basis for the diagnosis in this disease.[30] Based on the radiographic findings and the clinical features of the patient, our diagnosis was cherubism so we did not take an incisional biopsy.

The treatment of cherubism varies between individual cases. The treatment choices vary from conservative follow-up to more radical surgery according to the rate of progression of the lesion, complications, degree of destruction and emotional and functional disturbances caused by the lesion.[6] Because it has a self-limiting course and the lesions begin to regress after adolescence, conservative management is the preferred treatment.[31] On the other hand, some functional or emotional disturbances may require surgical intervention. Radiotherapy is contraindicated because of the high incidence of complications such as the formation of fibrosarcoma and osteoradionecrosis in the irradiated area.[32]

Orthodontic treatment is considered appropriate after growth is completed and after the regression of the disease.[2] However, Kau et al. performed a successful orthodontic treatment during the disease process to correct the malocclusion and reposition an impacted molar in a 15-year-old girl.[33] They stated that consultation with the orthodontist may be a better approach in providing a functional and aesthetic occlusion during the disease stages. In another caseed by Carvalho Silva et al. provided orthodontically assisted eruption of an unerupted maxillary left central incisor in a 16-year-old boy.[34] The chief complaint of our patient was mastication disturbance caused by buccal displacement of the mandibular second molars. Therefore, as a result of orthodontic consultation, the management of the occlusion was first planned as a distalization of mandibular first molars and lingualization of the mandibular second molars.

Medical treatment with calcitonin has been shown to prevent bone resorption by multinucleate giant cells in the cyst-like lesions, but the use of calcitonin therapy in patients with cherubism has been only rarely documented. Lannon and Earley observed therapeutic failure with the use of calcitonin injections for 6 months in a 7-year-old boy, and reported that no regression was observed.[31,35] Hart et al. used calcitonin for a year in a 6-year-old boy and obtained some degree of improvement, but they had to stop the treatment because of persistent nausea.[36] De Lange et al. performed a 15-month period of calcitonin therapy in an 11-year-old boy and achieved effective resolution of the lesions.[31] In another report, Etoz et al. administered calcitonin for a duration of 30 months in a 16-year-old boy.[37] They stated that radiographic regression of the lesions and growth of the patient had ended, and the patient was following up. However, the authors called attention to the fact that the remission could also have been associated with the natural course of the disease. In our case we decided to begin the calcitonin treatment with daily administration of 200 IU calcitonin via nasal spray until observing considerable regression of the lesions after endocrine consultation.

In conclusion, clinical features and radiographic findings are the basis for the diagnosis in cherubism; thus, it is important for the dentist to know these characteristic manifestations when assessing children with facial and dental problems. Radiographic interpretation plays a significant role in diagnosis in addition to assessing the extent of the lesions and it may prevent unnecessary invasive procedures such as incisional biopsies.

REFERENCES

1. Lima Gde M, Almeida JD, Cabral LA. Cherubism: clinicoradiographic features and treatment. J Oral Maxillofac Res 2010;1(2):e2.
2. Papadaki ME, Lietman SA, Levine MA, Olsen BR, Kaban LB, Reichenberger EJ. Cherubism: best clinical practice. Orphanet J Rare Dis 2012;7(Suppl 1):S6.
3. Chen H. Atlas of Genetic Diagnosis and Counseling. 2nd ed: New York: Springer; 2012. p.331-6.
4. Von Wowern N. Cherubism: a 36-year long-term follow-up of 2 generations in different families and review of the literature. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2000;90(6):765-72.
5. Kaugars GE, Niamtu J, Svirsky JA. Cherubism: diagnosis, treatment, and comparison with central giant cell granulomas and giant cell tumors. Oral Surg Oral Med Oral Pathol 1992;73(3):369-74.
6. White SC, Pharoah MJ. Other bone diseases. Oral Radiology: Principles and Interpretation. 7thed. St. Louis, Missouri: Elsevier Health Sciences; 2013. p.418-20.
7. Tsodoulos S, Ilia A, Antoniades K, Angelopoulos C. Cherubism: a case report of a three-generation inheritance and literature review. J Oral Maxillofac Surg 2014;72(2):405 e1-9.
8. Jones WA. Familial multilocular cystic disease of the jaws. Am J Cancer 1933;17(4):946-50.
9. Kozakiewicz M, Perczynska-Partyka W, Kobos J. Cherubism-clinical picture and treatment. Oral Dis 2001;7(2):123-30.
10. Fonseca LC, de Freitas JB, Maciel PH, Cavalcanti MG. Temporal bone involvement in cherubism: case report. Braz Dent J 2004; 15(1):75-8.
11. Hyckel P, Berndt A, Schleier P, Clement JH, Beensen V, Peters H, et al. Cherubism-new hypotheses on pathogenesis and therapeutic consequences. J Craniomaxillofac Surg 2005;33(1):61-8.
12. Silva GC, Gomez RS, Vieira TC, Silva EC. Cherubism: long-term follow-up of 2 patients in whom it regressed without treatment. Br J Oral Maxillofac Surg 2007;45(7):567-70.
13. Reade PC, McKellar GM, Radden BG. Unilateral mandibular cherubism: brief review and case report. Br J Oral Maxillofac Surg 1984;22(3):189-94.
14. Sohn B, Kim J, Shin N-Y, Kim C-H. CT findings of sporadic cherubism in a 6-year-old boy. J Korean Soc Radiol 2014;70(1):13-5.
15. Mehrotra D, Kesarwani A, Nandlal. Cherubism: case report with review of literature. J Maxillofac Oral Surg 2011;10(1):64-70.
16. Misra SR, Mishra L, Mohanty N, Mohanty S. Cherubism with multiple dental abnormalities: a rare presentation. BMJ Case Rep 2014;2014.
17. Lee JY, Jung YS, Kim SA, Lee SH, Ahn SG, Yoon JH. Investigation of the SH3BP2 gene mutation in cherubism. Acta Med Okayama 2008;62(3):209-12.
18. Ueki Y, Tiziani V, Santanna C, Fukai N, Maulik C, Garfinkle J, et al. Mutations in the gene encoding c-Abl-binding protein SH3BP2 cause cherubism. Nat Genet 2001;28(2):125-6.
19. Atalar M, Albayrak E, Erdinc P, Bulut S. Cherubism as a rare cause of bilateral expansion of the mandible: radiological manifestations. J HK Coll Radiol 2008;11:76-80.
20. Hitomi G, Nishide N, Mitsui K. Cherubism: diagnostic imaging and review of the literature in Japan. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1996;81(5):623-8.
21. Zachariades N, Papanicolaou S, Xypolyta A, Constantinidis I. Cherubism. Int J Oral Surg 1985;14(2):138-45.
22. Meng XM, Yu SF, Yu GY. Clinicopathologic study of 24 cases of cherubism. Int J Oral Maxillofac Surg 2005;34(4):350-6.
23. Silva EC, de Souza PE, Barreto DC, Dias RP, Gomez RS. An extreme case of cherubism. Br J Oral Maxillofac Surg 2002;40(1):45-8.
24. Roginsky VV, Ivanov AL, Ovtchinnikov IA, Khonsari RH. Familial cherubism: the experience of the Moscow Central Institute for Stomatology and Maxillo-Facial Surgery. Int J Oral Maxillofac Surg 2009;38(3):218-23.
25. Kalantar Motamedi MH. Treatment of cherubism with locally aggressive behavior presenting in adulthood: report of four cases and a proposed new grading system. J Oral Maxillofac Surg 1998;56(11):1336-42.
26. Colombo F, Cursiefen C, Neukam FW, Holbach LM. Orbital involvement in cherubism. Ophthalmology 2001;108(10):1884-8.
27. Pinheiro LR, Pinheiro JJ, Junior SA, Guerreiro N, Cavalcanti MG. Clinical and imagiological findings of central giant cell lesion and cherubism. Braz Dent J 2013;24(1):74-9.
28. Gorlin RJ, Goltz RW. Multiple nevoid basal-cell epithelioma, jaw cysts and bifid rib. A syndrome. N Engl J Med 1960;262:908-12.
29. Southgate J, Sarma U, Townend JV, Barron J, Flanagan AM. Study of the cell biology and biochemistry of cherubism. J Clin Pathol 1998;51(11):831-7.
30. Faircloth WJ, Edwards RC, Farhood VW. Cherubism involving a mother and daughter: case reports and review of the literature. J Oral Maxillofac Surg 1991;49(5):535-42.
31. de Lange J, van den Akker HP, Scholtemeijer M. Cherubism treated with calcitonin: report of a case. J Oral Maxillofac Surg 2007;65(8): 1665-7.
32. Pontes FS, Ferreira AC, Kato AM, Pontes HA, Almeida DS, Rodini CO, et al. Aggressive case of cherubism: 17-year follow-up. Int J Pediatr Otorhinolaryngol 2007;71(5):831-5.
33. Kau CH, Souccar NM, English JD, Kamel SG, Wong ME. The surgical and orthodontic management of cherubism in a growing child. J Craniomaxillofac Surg 2012;40(3):229-33.
34. Carvalho Silva E, Carvalho Silva GC, Vieira TC. Cherubism: clinicoradiographic features, treatment, and long-term follow-up of 8 cases. J Oral Maxillofac Surg 2007;65(3):517-22.
35. Lannon DA, Earley MJ. Cherubism and its charlatans. Br J Plast Surg 2001;54(8):708-11.
36. Hart W, Schweitzer DH, Slootweg PJ, Grootenhuis LS. Man with cherubism. Ned Tijdschr Geneeskd 2000;144(1):34-8.
37. Etoz OA, Dolanmaz D, Gunhan O. Treatment of cherubism with salmon calcitonin: a case report. Eur J Dent 2011;5(4):486-91.